pain and improve joint function in patients with end-stage post-traumatic OA. This result, combined with the observation that chondroprogenitor cells are active in osteoarthritic joints, suggests that altered loading creates an environment that promotes beneficial joint remodeling.
Conclusions: Taken together, these recent advances in understanding of how mechanical forces cause loss of articular cartilage, including identification of mechanically induced mediators of cartilage loss, and of how changing joint loading can promote joint remodeling provide the basis for new biologic and mechanical approaches to the prevention and treatment of all forms of OA.

I-6
RESEARCH TOOLS FOR THE STUDY OF ASPECTS OF THE EPIGENETICS OF OSTEOARTHRITIS

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Osteoarthritis (OA) is a degenerative joint disease characterised by degradation of articular cartilage as well as thickening of the subchondral bone and the formation of osteophytes at the joint margin. The aetiology of OA is complex with genetic, developmental, biochemical and biomechanical factors contributing to the disease process. Aberrant gene expression has clearly been shown in OA and epigenetic mechanisms may contribute to this. Epigenetic modifications may include: DNA methylation, histone modifications and non-coding RNA expression (both microRNA and long non-coding RNA). A number of studies have compared epigenetic modifications in OA and normal tissues and examined epigenetic mechanisms which impact upon the disease. Key to dissecting the function of epigenetics in OA is the methodology by which these changes can be measured. This workshop will explore aspects of the research tools which can be used for the study of epigenetics in OA. It will discuss tools which are appropriate in either the culture flask, or in limiting tissue samples. The scale of the study is also important since measuring genome wide changes requires different approaches from determining a single epigenetic mark. Quantification may also be key where different technologies show degrees of accuracy or linearity which may alter conclusions or require further validation. The workshop is not a lecture on epigenetics and OA, but rather a discussion of the tools available for researchers to apply in this area and their strengths and weaknesses.

I-7
USING ZEBRAFISH TO PROBE THE GENETICS OF OSTEOARTHRITIS

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Purpose: The purpose of our work is to ascertain the extent to which zebrafish can be used as an animal model to dissect how osteoarthritis susceptibility genes affect cell behaviour in the formation and maintenance of joints.
Methods: Using BAC recombineering we have generated a number of transgenic lines in which fluorescent reporters are expressed under the control of promoters linked to cartilage biology, for example Type 2 and Type X Collagens and Gdf5, as well as reporters for the activity of a number of signalling pathways including Wnt and Hedgehog; allowing us to visualise cell behaviour in real time in the translucent fish. We have used a number of histological and immunohistochemical methods along with electron microscopy and microCT to characterise a number of events in zebrafish cartilage development, joint formation and during skeletal ageing. We have also generated Finite Element models that allow us to visualise the biomechanical strains experienced in zebrafish jaw elements resulting from the action of their associated muscles.
Results: Using a combination of techniques we show that in the zebrafish normal joint morphogenesis requires muscle action, and occurs through changes to cell organisation and orientation. We show using Finite Element Analysis that positions of high biomechanical strain in the zebrafish joint overlap regions of high Wnt signalling activity, and show that Wnt signalling is required downstream of muscle activity for correct joint morphogenesis. We also show that cartilage in ageing fish show a number structural and biochemical changes some of which are reminiscent of those seen in osteoarthritis in other animal models and in human cartilage
Conclusions: Taken together we conclude that zebrafish can be a useful animal model to dissect the role of osteoarthritis susceptibility genes in the behaviour of chondrocytes during joint development, homeostasis and ageing in normal and pathological situations.

I-8
PROTEOMICS AND BIOMARKERS IN OSTEOARTHRITIS

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Purpose: The application of modern proteomic techniques to disease states affords the opportunity to identify deregulated pathways that contribute to pathogenesis. These discoveries in turn may lead to new therapeutic targets, as well as "wet" biomarkers that aid in diagnosis, prognosis and the prediction of treatment responses. Building on the concept that osteoarthritis (OA) is a disease of all joint structures (synovium, cartilage and bone), and that synovial fluid (SF) may represent of synthesis of inputs from these structures, we compared the proteomic profile of knee joint SF from patients with early and late stage OA to unaffected controls by 2-dimensional gel electrophoresis and mass spectrometry. In our recent publication, using this relatively unbiased approach, 66 proteins were reported as differentially represented in healthy vs. OA SF (1). Pathway analysis identified three biologic processes among these proteins: the complement and coagulation systems and the acute phase response. Interestingly, early and late OA manifested a very similar proteomic profile. Together, these findings suggest the osteoarthritic disease processes involves activation of inflammatory pathways that are well-established by the time patients are diagnosed. This presentation will explore 1) the relative contribution of joint tissues to the SF OA proteome, including cartilage and synovium, 2) how proteomics can illuminate the pathogenesis of OA to identify therapeutic targets, 3) validation of proteomic discovery findings using multiplexed selected reaction monitoring (SRM) mass spectrometry peptide assays and 4) translation of SF protein biomarkers to quantitative serum based assays to predict disease progression in OA patients. At the end of this presentation, attendees should understand some of the major protein constituents of OA SF and how knowledge of this proteome may inform pathogenesis and biomarker development for this difficult disease.

1. Ritter SY, Subbaiah R, Bebek G, Crish J, Scanzello CR, Krastins B, Sarracino D, Lopez MF, Crow MK, Aigner T, Goldring MB, Goldring SR, Lee DM, Gobezie R, and Aliprantis AO. Proteomic analysis of synovial fluid from the osteoarthritic knee: comparison with transcriptome analyses of joint tissues. Arthritis Rheum 2013;65:981–992.

I-9
HOW LIFESTYLE FACTORS INFLUENCE THE DEVELOPMENT AND PROGRESSION OF OA

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Purpose: Osteoarthritis (OA) is the most common worldwide disease of joints and its prevalence is growing. The worldwide obesity epidemic in older adults is fueling an increase in many chronic diseases, including osteoarthritis. This presentation will focus on knee OA, which is the most prevalent form of OA and a major cause of arthritis-related functional loss and disability.
The American College of Rheumatology 2012 recommendations recognize lifestyle factors, including weight loss and physical activity, as primary nonpharmacologic therapies for OA. Obesity has long been a recognized risk factor for the development of knee OA. Obesity contributes to OA through joint load, altered gait, and impaired muscle performance. Importantly weight influences the course of disease progression. Longitudinal cohort data provide evidence for a dose response relationship between weight change and function. Notably, 45% of adults with a weight loss $\geq$10% had a clinically meaningful improvement in WOMAC function. Randomized controlled clinical trials (RCT) support the effectiveness of weight loss to improve function in adults with knee OA. RCT evidence in obese knee OA patients demonstrated a 10% weight loss% could improve self-reported function by more than 25%.

Physical activity is a more recent addition to non-pharmaceutical interventions. In 2008, the US published federal guidelines recommending adults with arthritis participate in 150 minutes of moderate activity each week accumulated in sessions lasting at least 10 minutes. Physical activity benefits are supported by dose-response relationships with better physical function based on longitudinal cohort studies. RCTs demonstrate the effectiveness of both exercise interventions and resistance training to improve function and reduce disability in adults with knee OA. Recent RCTs provide insight into the synergy between weight loss and physical activity in knee OA. Exercise alone and weight loss alone were each effective to improve function; however weight loss plus exercise had the greatest effect.

These studies support interventions which increase moderate intensity activity. However, many adults are not candidates to engage in moderate intensity activities due to health limitations. What strategies are available to these adults? Recent work demonstrated sedentary behavior is a significant risk factor for functional loss in adults including those with knee OA. Importantly, this relationship is independent of obesity status and of time spent in moderate intensity activities. These findings support replacing sedentary time with light activity to improve health outcomes in adults with knee OA who cannot perform/increase moderate intensity activities.

Taken as a whole, life style interventions provide important strategies to prevent knee OA and mitigate its consequences. Weight control can reduce the risk of developing knee OA. For overweight adults with knee OA, weight loss can effectively improve function. Engaging in physical activity of moderate intensity can improve function and reduce disability. Weight loss combined with increased activity provides added benefits for overweight adults. While the benefits of physical activity are substantial, not all older adults are candidates to engage in moderate intensity activities. An alternative strategy is to replace time spent in sedentary behavior with light intensity activities to improve function.

I-10
BE IT RESOLVED: PLAIN RADIOGRAPHY OR MRI – WHICH IS BETTER IN ASSESSING OUTCOME IN CLINICAL TRIALS?

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Purpose: Imaging in clinical trials is commonly used to evaluate the efficacy of a therapeutic intervention, but also for subject eligibility and safety. The results of clinical trials can support decision making in DMOAD development, by ascertaining treatment effects on joint structure, potentially before these translate to clinical benefits. This debate will focus on the use of radiography and magnetic resonance imaging (MRI) in research trials and in clinical trials of knee osteoarthritis. Depending on the context, the strength and weaknesses of each imaging technique will be highlighted and performance will be compared.

Methods: The authors have performed a full-text literature on imaging of the knee, with a focus on bone and cartilage, adding primary experience in the implementation of imaging methods in clinical trials, and results presented at recent conferences.

Results: The authors will present summary data on the reliability (consistency, test-retest precision) of radiographic measurement of joint space width (JSW) and cartilage thickness with MRI. They will address the construct, concurrent and predictive validity of both methods, compare their sensitivity to change in knee OA in studies that examined JSW and cartilage thickness change in the same subjects, and highlight the specific potential and the limitations of each imaging technique. Finally, the correlation with clinical outcomes and the response to treatment will be addressed.

Conclusion: Current imaging methodologies provide powerful tools for evaluating morphological and compositional aspects of most articular tissues, capturing longitudinal change with reasonable to excellent sensitivity. Radiography and MRI are complementary imaging techniques; each has specific strengths and weaknesses that depend on the specific context of the questions asked. When employed properly, each of them involves potential for ascertaining treatment effects on joint structure, potentially over shorter time scales than required for demonstrating effects on clinical outcomes.

I-11
NON-CARTILAGE CHANGES VISUALIZED BY MRI AND RISK FOR OA DEVELOPMENT/PROGRESSION

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Non-cartilaginous tissues that may be affected in osteoarthritis (OA) include the subchondral bone, synovium, fibrocartilage, ligaments and muscles. Due to its capability to visualize pathology in different tissues with excellent contrast, magnetic resonance imaging (MRI) provides high-resolution and multiplanar assessment of the bone and soft tissues mentioned above. The use of semiquantitative and quantitative MRI biomarkers of non-cartilaginous tissues in clinical and epidemiological OA studies is reviewed. Bone marrow lesions (BMLs) are defined on MRI as non-cystic subchondral areas of ill-defined hyperintensity on fluid-sensitive spin-echo sequences, and were shown to be associated with incidence and progression of knee OA, including progression of MRI-detected cartilage loss and radiographically detected joint space narrowing (JSN). MRI is the best imaging method for the detection and grading of BMLs. The close relationship between BMLs and cartilage damage in the same region of the joint was extensively demonstrated in previous studies. BMLs represent a highly variable feature in patients with or at risk for development of knee OA, as their size may increase or decrease over time. This is of relevance since it was demonstrated that the fluctuation of BML size over time seems to have a direct effect on progression of disease assessed on a subregional basis. MRI is also capable to accurately assess the morphology of the subchondral bone, especially in the detection of any degree of subchondral flattening or depression, also known as subchondral bone attrition. A strong association exists between subchondral bone attrition and subchondral BMLs in the same region of the knee, and the association increases with BML size. Further, it was demonstrated that attrition represents a risk factor for progression of cartilage loss in the same compartment of the knee. Meniscal damage including tears and maceration, as well as meniscal extrusion, were shown to be independently associated with incidence and progression of OA, including progression of radiographically-detected JSN and MRI-detected cartilage loss. MRI is the method of choice in the assessment of meniscal damage and meniscal extrusion, with multiplanar spin-echo techniques being the most appropriate for their detection and grading. Although synovitis in OA is thought to be a secondary phenomenon related to cartilage deterioration, its importance in the OA process is well recognized. Several methods for detecting and quantifying synovitis with non-enhanced and contrast-enhanced MRI are available. Synovitis should be ideally assessed and quantified using gadolinium-enhanced MRI, although surrogate markers for synovitis on non-enhanced MRI are available and are widely utilized in published studies. There is little evidence that synovitis is not only a secondary phenomenon in patients with knee OA but may also play a role in progression of disease. This relationship remains to be demonstrated in large longitudinal studies. Alternatively, synovitis can be evaluated in combination with effusion on fluid-sensitive sequences but differentiation between inflamed synovium and joint fluid filling the joint cavity surrounded by synovium may be difficult. Ligament injury can be accurately depicted by multiplanar MRI assessment of joints. In the knee, it was demonstrated that cruciate ligament deficiency secondary to tears increase the risk for incidence or progression of OA. Further, it was shown that collateral ligaments at both distal and proximal interphalangeal joints may play a role in early stages of OA. The role of other non-cartilaginous tissues accurately assessed by MRI, such as the acetabular labrum (hip) and quadriceps muscle (knee), and their relationship with structural deterioration in these joints was also demonstrated in a few studies. This presentation reviews the role of non-cartilage structures, as well as pathology in these structures, in the development and/or progression of OA, focusing in the knee joint, based on the evidence in the literature.

I-12
GENETICS/GENOMICS IN OSTEOARTHRITIS

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In this year review recent developments in genetics/genomics of osteoarthritis (OA) are discussed to improve our understanding of OA pathophysiology. In OA genetics, a meta-analysis of genome wide association studies (GWAS) revealed novel loci for hip OA, among which